Treatment of Locally Advanced Pancreatic Ductal Adenocarcinoma

Andrew P. Loehrer · Cristina R. Ferrone

Department of Surgery, Massachusetts General Hospital, Boston, Mass., USA

Key Words

Pancreas cancer · Chemotherapy · Radiotherapy · Chemoradiation · Combined modality therapy

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is increasingly common and a leading cause of cancer-related mortality. Surgery remains the only possibility for cure. Upwards of 40% of patients present with locally advanced PDAC (LA-PDAC), where management strategies continue to evolve. In this review, we highlight current trends in neoadjuvant chemotherapy, surgical resection, and other multimodality approaches for patients with LA-PDAC. Despite promising early results, additional work is needed to more accurately and appropriately tailor treatment for patients with LA-PDAC.

© 2016 S. Karger AG, Basel

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is increasingly common and the fourth leading cause of cancer mortality in the United States, with overall 5-year survival of <4% [1]. Surgical resection remains the only potential for cure. Unfortunately, <20% of patients present with resectable disease and 45% present with overtly metastatic disease [2]. Increasing attention has been placed

on the remaining 40% of patients with locally advanced PDAC (LA-PDAC). Although the overall prognosis for pancreatic cancer remains quite poor, increased use of more effective multimodality therapy has allowed for significantly improved survival for even the most challenging cases of LA-PDAC [3]. With this review, we aim to summarize recent advances in the management and treatment of patients with LA-PDAC as well as highlighting some promising new directions moving forward.

Significance of Resectability

For patients with LA-PDAC, surgical consideration rests on the ability to obtain negative resection margins. A recent analysis compared survival between wide R0 resections, R0 resections with tumor within 1 mm of margin and R1 resections. Median survival for patients with wide R0 resections was significantly greater than in those with margins of <1 mm or R1 resections (35 vs. 16 vs. 14 months, respectively; $p < 0.001$) [4]. Yet preoperative determination of resectability has been challenging and as such multiple definitions of locally advanced or borderline resectable PDAC have been established. Early radiologic definitions deemed tumors locally advanced if abutting the celiac trunk or superior mesenteric artery or involvement of the portal vein or superior mesenteric vein [5]. Due to the heterogeneity of definitions The Univer-

sity of Texas MD Anderson Cancer Center, Americas Hepatopancreaticobiliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract and the National Comprehensive Cancer Network have modified these definitions based on vascular involvement [6–9]. At our center, we consider locally advanced tumors as cancers with (1) no distant metastasis, (2) absence of blood flow through the SMV and/or portal vein lumen or venous involvement not amenable to reconstruction, (3) involvement of the common hepatic artery or superior mesenteric artery over >180 degrees of the vessel circumference, (4) any celiac abutment or (5) aortic or inferior vena cava invasion or encasement. The utility of these traditional definitions is under ongoing evaluation as we determine the accuracy of radiographic imaging following neoadjuvant therapy (discussed below). Inclusion of additional factors beyond radiology, including biomarkers such as carbohydrate antigen 19-9 or SMAD4 mutation status, have also been proposed to refine our present classification system and guide more appropriate treatment [10, 11].

Neoadjuvant Chemotherapy

Until recently, nearly 30% of patients with LA-PDAC have progression of disease or metastasis during early cycles of treatment and only 30% of patients were converted from unresectable to surgical candidates after the receipt of chemotherapy and/or chemoradiation [12, 13]. However, multiple recent studies have provided promising results that these numbers could be shifting with neoadjuvant chemotherapy and/or chemoradiation.

FOLFIRINOX

The ACCORD-11 trial demonstrated an improved survival associated with FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil and leucovorin) versus gemcitabine in patients with metastatic disease [14]. Since this time, multiple additional groups have looked to the regimen as a potential neoadjuvant therapy for patients with borderline resectable or LA-PDAC. A recent cohort of that included 188 patients undergoing resection for PDAC compared results for those with LA/borderline tumors who received neoadjuvant FOLFIRINOX and those who had an operation followed by adjuvant gemcitabine [15]. Despite post-FOLFIRINOX imaging suggesting that 70% of patients had persistent LA/borderline disease, pathology demonstrated a 92% R0 resection rate and significantly lower rates of positive lymph nodes and perineural or

lymphatic invasion as compared to those who underwent an operation alone. These findings are consistent with other studies suggesting that radiologic indicators of resectability are unreliable after receipt of neoadjuvant chemotherapy or chemoradiation [16]. Although the study had a relatively short median follow-up time of 11 months, the FOLFIRINOX-treated cohort was associated with improved overall survival ($p = 0.008$). Other groups have demonstrated similarly encouraging results [17, 18]. Christians et al. [18] showed resection in 83% of patients after neoadjuvant FOLFIRINOX and chemoradiation, with an R0 resection in all 12 patients resected and node positivity in only 17% of patients. Long-term follow-up of these patients will hopefully elucidate if promising early results in resectability translate into an actual survival benefit as seen with neoadjuvant FOLFIRINOX.

Although FOLFIRINOX has shown promising results in terms of overall survival and conversion of locally advanced tumors to potentially resectable, the regimen is also associated with higher rates of neutropenia (45%), febrile neutropenia (5.4%), thrombocytopenia (9.1%) and diarrhea (12.7%) [11]. As such, most use of this regimen has been limited to patients with relatively good functional status (ECOG performance status 0 or 1). Subsequent analyses of the Accord 11 trial noted persistently higher rates of diarrhea in the FOLFIRINOX cohort, but otherwise an actual longer time until deterioration of quality of life as compared to patients in the gemcitabine arm [19]. Others have slightly modified the FOLFIRINOX regimen to be more tolerable, including elimination of bolus 5-FU and adding prophylactic pegfilgrastim [20, 21]. Such modified regimens have shown to be safe and effective with Blazer et al. [21] reporting subsequent resection possible in 72% of patients with an R0 resection rate in 86.4%.

Gemcitabine-Based Therapy

Gemcitabine has been a staple agent in the treatment of PDAC since the CONKO-001 trial. The trial compared adjuvant chemotherapy with gemcitabine to observation alone after an R0 or R1 resection for PDAC. The gemcitabine group had a median survival of 13.4 months compared to 6.9 months in the observation alone group ($p < 0.001$) [22].

Combination therapy of gemcitabine and nab-paclitaxel has also been investigated for LA-PDAC following the Phase 3 randomized trial for patients with metastatic PDAC [23]. The combination was associated with a 2-month longer median overall survival (hazard ratio for death 0.72, 95% CI 0.62–0.83; $p < 0.001$), but also higher

rates of peripheral neuropathy and myelosuppression than gemcitabine alone. Use of gemcitabine plus nab-paclitaxel in the neoadjuvant setting for LA-PDAC is still limited to case reports but trials are presently underway [24]. Furthermore, efficacy of gemcitabine plus nab-paclitaxel compared with FOLFIRINOX is yet to be evaluated on a head-to-head basis.

Barugola et al. [25] retrospectively examined the utilization of gemcitabine-based neoadjuvant chemotherapy and subsequent surgical outcomes. Of the 41 patients who received neoadjuvant therapy, nearly 71% went on to have an R0 resection compared to 59.7% of patients who went directly to the operating room ($p = 0.20$). Patients receiving neoadjuvant therapy had lower nodal positivity compared to upfront surgery (31.7 vs. 86.2%, respectively; $p < 0.001$), had comparable rates of postoperative morbidity (41.5 vs. 33.7%, respectively; $p = 0.390$) and a comparable median survival from the time of resection (35 vs. 27 months, respectively; $p = 0.740$). Although this report did not follow all patients receiving neoadjuvant therapy, the study provided encouraging data that patients with locally advanced disease can benefit from and comparable outcomes to those who present with initially resectable disease.

In a single-institutional series, Leone et al. [26] evaluated efficacy of neoadjuvant gemcitabine with oxaliplatin (GEMOX) followed by neoadjuvant chemoradiation for patients with LA-PDAC. Nine of 15 patients with borderline resectable disease ultimately proceeded to an R0/R1 resection. The median survival for patients undergoing resection was 31.5 months compared to 12.3 months for unresected patients ($p < 0.001$). Another multi-institutional phase 2 study of neoadjuvant GEMOX with radiation examined 68 patients with resectable or borderline disease [27]. Forty-three of these patients underwent resection, 84% with R0 resection and median survival of 34.6 months. Trials comparing gemcitabine with nab-paclitaxel or oxaliplatin to FOLFIRINOX have also yet to be completed.

Neoadjuvant Chemoradiation

Given the significance of having negative surgical margins, neoadjuvant chemoradiation (CRT) has long been promoted for the treatment of LA-PDAC [28, 29]. Evaluation of the Surveillance, Epidemiology and End Results registry from 1994 to 2003 found that patients receiving neoadjuvant CRT have significantly higher rates of survival relative to non-neoadjuvant CRT (hazard ratio 0.55,

95% CI 0.38–0.79; $p = 0.001$) and adjuvant radiation therapy (hazard ratio 0.63, 95% CI 0.45–0.90; $p = 0.03$) [30]. Furthermore, neoadjuvant CRT is not only associated with improved survival, but also a significantly lower cost than surgery-first approaches [31].

However, chemoradiation alone in the absence of neoadjuvant chemotherapy appears to be suboptimal. Arvold et al. [32] examined 70 consecutive patients with unresectable or LA-PDAC who received either chemoradiation alone or neoadjuvant gemcitabine-based chemotherapy followed by chemoradiation. Twenty percent of patients in both groups subsequently underwent surgical resection. Patients receiving chemotherapy in addition to chemoradiation had a median survival of 18.7 versus 12.4 months ($p = 0.02$) for patients receiving chemoradiation alone. Other studies, although underpowered, suggested that the addition of chemoradiation to gemcitabine therapy conferred a marginal survival benefit with comparable toxicity profiles [33, 34]. Correspondingly, CRT usually follows induction chemotherapy which allows for identification of patients, approximately 30%, with initially undetected metastatic disease [35, 36]. The optimal chemotherapeutic regimen and radiation dosages also remain in question. In their systematic review, Gillen et al. [13] highlighted that the majority of published studies including radiotherapy doses between 40 and 60 Gy, with most patients receiving 1.8–2.0 Gy/fraction.

The histological response of tumors to neoadjuvant chemoradiation has been shown to be an important prognostic factor in which patients with complete pathologic response have improved overall survival [37, 38]. However, the timing between completion of radiation and surgical resection remains unclear. In a retrospective analysis, Chen et al. [39] examined pathologic response of patients having received different intervals of chemotherapy after completion of neoadjuvant chemoradiation and before surgical resection. Compared to patients who received between 0–10 weeks of chemotherapy between radiation and surgery, this study found that patients undergoing >20 weeks of chemotherapy between chemoradiation and surgery had a significant increase in rates of R0 resection, progression-free survival and overall survival.

Few studies have explicitly compared the chemotherapy use in conjunction with radiotherapy. Takai et al. [40] evaluated patients with LA-PADC who received neoadjuvant chemoradiation with either 5-fluorouracil and cisplatin or gemcitabine. Eight patients remained unresectable after neoadjuvant chemoradiotherapy, 6 patients (42%) received 5-FU/cisplatin and 2 patients (11%) re-

ceived gemcitabine. Toxicities of preoperative radiation as well as survival of resected patients were comparable between both 5-FU/cisplatin and gemcitabine cohorts. Another study out of France followed 61 patients treated with 5-FU/cisplatin and radiation, with only 23 patients (38%) who demonstrated an objective response allowing re-exploration and only 13 patients (21%) undergoing R0/R1 resection [41]. Median survival for those undergoing a resection was 28 and 20 months for the 10 patients who underwent a palliative procedure. Although 5-FU and gemcitabine have been the most widely used agents, other phase I trials and case series have been presented using additional or alternative chemosensitizers including capecitabine, bevacizumab and paclitaxel [42–44]. The optimal combination is under ongoing investigation.

Surgical Resection and Intraoperative Therapy

As previously discussed, the traditional extent of disease denoting unresectable disease includes tumor encasement of the superior mesenteric artery, celiac trunk or hepatic artery. Portal venous involvement becomes unresectable when there is complete occlusion with the development of multiple collaterals which cannot be reconstructed. Given the significant improvement in survival in patients resected as compared to those left with unresected primary tumors, groups have studied the feasibility of vascular resection and reconstruction. Yekebas et al. [45] evaluated 585 patients who underwent a potentially curative pancreatic resection with ($n = 136$) or without ($n = 449$) vascular reconstruction. Of those undergoing vascular resection, 128 (94%) of these involved the mesentericoportal axis and 13 (10%) involved the hepatic artery or superior mesenteric artery. Five patients had both venous and arterial reconstruction. Their results suggested comparable morbidity and mortality in patients undergoing en bloc resection of LA-PDAC relative to those not undergoing vascular resection. Similarly, Tseng et al. [46] examined patients undergoing pancreatic resection with ($n = 141$) and without ($n = 181$) vascular resection over a 12-year period at the M.D. Anderson Cancer Center. These too were also predominantly venous resection and reconstructions, with concomitant hepatic artery resections in 17 of the patients (12%). Patients undergoing vascular reconstruction had comparable major morbidity and mortality rates. Median survival for patients undergoing pancreaticoduodenectomy with vascular resection was not significantly different than patients having resection without reconstruction (23.4 vs.

26.5 months, respectively; $p = 0.18$). However, acute thrombosis of the portal venous reconstruction following pancreatic resection is not only associated with increased perioperative mortality (22.2 vs. 4.6%; $p = 0.023$), but is also associated with a decreased median survival (7.1 vs. 15.9 months; $p = 0.011$) even when non-fatal [47].

While the cumulative literature on feasibility and efficacy of venous reconstruction are promising, outcomes following arterial resection remain in question. A recent meta-analysis found that pancreatectomy with simultaneous arterial resection was associated with increased perioperative mortality (OR 5.04, 95% CI 2.69–9.45; $p < 0.001$), as well as decreased survival at 1 year (OR 0.49, 95% CI 0.31–0.78; $p = 0.02$) and at 3 years (OR 0.39, 95% CI 0.17–0.86; $p = 0.02$) [48]. Bockhorn et al. [49] shared their experience with arterial resection and reconstruction, finding significantly higher rates of major complications, higher mortality and lower rates of R0 resections. Yet, median survival for patients undergoing arterial reconstruction was comparable to those patients who underwent pancreatic resection without concomitant vascular resection and significantly better than patients who underwent palliative bypass alone. Thus, authors appropriately caution that marginal benefits in overall survival must be very carefully weighed, on a case-by-case basis, against the considerable perioperative morbidity and mortality associated with arterial vascular reconstruction.

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) has been studied extensively over the past few decades. Patients receiving IORT at our institution have usually already received full dose external beam radiation. IORT is then administered as a single dose of radiation focally targeted at the surgical margin or residual disease. This modality has great appeal in being able to shield healthy tissue from radiation while potentially reducing risk of wider external beam radiation toxicity. Previous publications from the Massachusetts General Hospital have found favorable oncologic and survival outcomes in select patients with unresectable pancreatic cancer [50, 51]. Data on the use of IORT as an adjunct to surgical resection for LA-PDAC is inconclusive, with the majority of studies suggesting no survival benefit [52–55]. A more recent Japanese study of 210 patients treated with resection and IORT, in conjunction with chemotherapy and/or external beam radiation, resulted in 2-year local control rates of 87.1 and 74.6% following R0 and R1 resections, respectively [56]. There was no clear association between dose of IORT (20, 25, or 30

Gy) and local control or overall survival. R0 versus R1 resection and use of adjuvant chemotherapy was associated with an improved overall survival. Another multi-institutional European cohort found a 5-year local control rate in 23.3% of patients with significantly greater local control and survival in patients who also received preoperative radiotherapy (median survival 30 months) versus EBRT alone (median survival 22 months, $p < 0.001$) or IORT alone (median survival 13 months, $p < 0.001$) [57]. However, these authors as well acknowledge the limitations of a 20-year study period and significant improvements in IORT technology, adjunctive chemotherapy regimens and improved surgical techniques over this period, which limits generalizability of findings in the setting of present-day, multimodality treatment. In general, toxicities related to IORT are limited and include colitis, gastrointestinal bleeding, epigastric discomfort and ileus [58, 59]. Multiple series from select institutions, including a propensity score-matched analysis, have suggested no significant difference in perioperative complications with the use of IORT [60, 61].

Intraoperative Electroporation

Newer technologies have also been increasingly applied with hopes of increasing local control at the time of surgery. Irreversible electroporation (IRE) utilizes short, high-voltage pulses to tissue causing increased cellular membrane permeability and tumor ablation [62]. Recent multi-institutional studies integrating IRE into the multimodality treatment of LA-PDAC have demonstrated improvements in local control and survival with progression-free and median overall survival of 11 and 22 months, respectively [63, 64]. Complication rates in these early experiences appear to be comparable to outcomes following resection and multimodality therapy in the absence of IRE. The effective incorporation of this technique into newer chemotherapeutic and radiation-based regimens is an area of ongoing investigation.

Adjuvant Therapy

Studies from the United States as well as Italy suggest that both perioperative and overall survival following surgery have improved significantly over the past 25 years [65, 66]. Adjuvant chemotherapy has become a mainstay following resection of PDAC and the role of adjuvant chemoradiation remains to be clearly defined [67–71]. Many found flaws in the adjuvant chemoradiation study designs and analyses, resulting in ongoing trials such as

RTOG 0848 to evaluate the role of modern chemoradiation regimens following surgical resection [72]. However, no studies to date have examined the efficacy of chemotherapy or chemoradiation in patients with LA-PDAC following neoadjuvant treatment and resection. Much more data on adjuvant after neoadjuvant therapy will surface in the coming years as the utilization of neoadjuvant protocols increases.

Future Directions

Advances in imaging technology have improved the diagnosis and staging of patients with pancreatic cancer, and neoadjuvant therapy has demonstrated promising early results; however, the prognosis of patients presenting with LA-PDAC remains poor. Currently utilized helical CT scanning has been readily shown to be inadequate at assessing the true response to neoadjuvant therapy [15]. Additional imaging modalities are needed to evaluate true response to treatment, provide more accurate prognostic information and guide optimal treatment. Furthermore, novel tumor markers or other prognostic factors might also better guide therapeutic options, including determination of who might best benefit from surgical resection. Fluorouracil and gemcitabine-based chemotherapy has been the mainstay in treatment. Newer regimens including FOLFIRINOX, GEMOX and Gemcitabine with paclitaxel are still in their infancy. Newer drugs and incorporation of immunotherapy, including ipilimumab or erlotinib, may provide additional benefit though data for LA-PDAC remains to be seen [73, 74].

Conclusions

Pancreatic cancer is increasingly common and up to 40% of cases are locally advanced at the time of presentation. The incorporation of neoadjuvant chemotherapy and more aggressive surgical resections have provided incremental improvement in survival but overall prognosis for majority of patients remains poor. Ongoing study of newer medical therapy, as well as prognostic markers is needed to more accurately and appropriately tailor treatment for individual patients.

Disclosure Statement

The authors have no disclosures or conflicts to report.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ: Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
- Vincent A, Herman J, Schulick R, Hruban RH, Goggins M: Pancreatic cancer. *Lancet* 2004;27:1049–1057.
- Truty MJ, Thomas RM, Katz MH, Vauthey JN, Crane C, Varadhachary GR, Wolff RA, Abbruzzese JL, Lee JE, Fleming JB: Multimodality therapy offers a chance for cure in patients with pancreatic adenocarcinoma deemed unresectable at first operative exploration. *J Am Coll Surg* 2012;215:41–51; discussion 51–52.
- Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V, Hong TS, Kwak EL, Lauwers GY, Ryan DP, Wargo JA, Lillemoe KD, Ferrone CR: Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a 'true' R0 resection? *Ann Surg* 2013;257:731–736.
- Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J: Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR Am J Roentgenol* 1997;168:1439–1443.
- Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, Lee JE, Pisters PW, Evans DB, Wolff RA: Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;13:1035–1046.
- Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF: Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–846; discussion 846–848.
- Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC: Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1727–1733.
- Katz MH, Marsh R, Herman JM, Shi Q, Collison E, Venook AP, Kintler HL, Alberts SR, Philip P, Lowy AM, Pisters PW, Posner MC, Berlin JD, Ahmad SA: Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol* 2013;20:2787–2795.
- Katz MHG, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF: Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–846; discussion 846–848.
- Evans DB, Erickson BA, Ritch P: Borderline resectable pancreatic cancer: definitions and the importance of multimodality therapy. *Ann Surg Oncol* 2010;17:2803–2805.
- He J, Page AJ, Weiss M, Wolfgang CL, Herman JM, Pawlik TM: Management of borderline and locally advanced pancreatic cancer: where do we stand? *World J Gastroenterol* 2014;20:2255–2266.
- Gillen S, Schuster T, Meyer zum Büschenfelde C, Friess H, Kleeff J: Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267.
- Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
- Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, Sabbatino F, Santos DD, Allen JN, Blaszkowsky LS, Clark JW, Faris JE, Goyal L, Kwak EL, Murphy JE, Ting DT, Wo JY, Zhu AX, Warshaw AL, Lillemoe KD, Fernández-del Castillo C: Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015;261:12–17.
- Katz MH, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, Wang H, Abbruzzese J, Pisters PW, Vauthey JN, Charnsangavej C, Tamm E, Crane CH, Balachandran A: Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 2012;118:5749–5756.
- Peddi PF, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM, Suresh R, Lockhart AC, Wang J, Menias C, Gao F, Linehan D, Wang-Gillam A: Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. *JOP* 2012;13:497–501.
- Christians KK, Tsai S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, Kelly T, Erickson B, Wang H, Evans DB, George B: Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 2014;19:266–274.
- Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T: Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013;31:23–29.
- Mahaseth H, Brucher E, Kauh J, Hawk N, Kim S, Chen Z, Kooby DA, Maithel SK, Landry J, El-Rayes BF: Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 2013;42:1311–1315.
- Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, Wuthrick E, Williams TM, Reardon J, Ellison EC, Bloomston M, Bekaii-Saab T: Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. *Ann Surg Oncol* 2015;22:1153–1159.
- Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutterer K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H: Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized control trial. *JAMA* 2007;297:267–277.
- Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjuland SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–1703.
- Olowokure O, Torregroza-Sanchez MP, Bedoya-Apaez ID: Gemcitabine plus nab-paclitaxel with chemoradiation in locally advanced pancreatic cancer (LAPC). *J Gastrointest Oncol* 2013;4:E16–E18.
- Barugola G, Partelli S, Crippa S, Capelli P, D'Onofrio M, Pederzoli P, Falconi M: Outcomes after resection of locally advanced or borderline resectable pancreatic cancer after neoadjuvant therapy. *Am J Surg* 2012;203:132–139.
- Leone F, Gatti M, Massucco P, Colombi F, Sperti E, Campanella D, Regge D, Gabriele P, Capussotti L, Aglietta M: Induction gemcitabine and oxaliplatin therapy followed by a twice-weekly infusion of gemcitabine and concurrent external-beam radiation for neoadjuvant treatment of locally advanced pancreatic cancer: a single institutional experience. *Cancer* 2013;119:277–284.
- Kim EJ, Ben-Josef E, Herman JM, Bekaii-Saab T, Dawson LA, Griffith KA, Francis IR, Greenon JK, Simeone DM, Lawrence TS, Laheru D, Wolfgang CL, Williams T, Bloomston M, Moore MJ, Wei A, Zalupski MM: A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer* 2013;119:2692–2700.
- A multi-institutional comparative trial of radiation therapy alone and in combination with 5-fluorouracil for locally unresectable pancreatic carcinoma. The gastrointestinal tumor study group. *Ann Surg* 1979;189:205–208.

- 29 Douglass HO: Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *Gastrointestinal tumor study group. J Natl Cancer Inst* 1988;80:751–755.
- 30 Stessin AM, Meyer JE, Sherr DL: Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *Int J Radiat Oncol Biol Phys* 2008;72:1128–1133.
- 31 Abbott DE, Tzeng CW, Merkow RP, Cantor SB, Chang GJ, Katz MH, Bentrem DJ, Bilimoria KY, Crane CH, Varadhachary GR, Abbruzzese JL, Wolff RA, Lee JE, Evans DB, Fleming JB: The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. *Ann Surg Oncol* 2013;20(suppl 3):S500–S508.
- 32 Arvold ND, Ryan DP, Niemierko A, Blaszkowsky LS, Kwak EL, Wo JY, Allen JN, Clark JW, Wadlow RC, Zhu AX, Fernandez-del Castillo C, Hong TS: Long-term outcomes of neoadjuvant chemotherapy before chemoradiation for locally advanced pancreatic cancer. *Cancer* 2012;118:3026–3035.
- 33 Cardenes HR, Moore AM, Johnson CS, Yu M, Helft P, Chiorean EG, Vinson J, Howard TJ, Stephens AW, Tai DF, Loehrer PJ Sr: A phase II study of gemcitabine in combination with radiation therapy in patients with localized unresectable, pancreatic cancer: a Hoosier oncology group study. *Am J Clin Oncol* 2011;34:460–465.
- 34 Loehrer PJ, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB 3rd: Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an eastern cooperative oncology group trial. *J Clin Oncol* 2011;29:4105–4112.
- 35 Krishnan S, Rana V, Janjan NA, Varadhachary GR, Abbruzzese JL, Das P, Delclos ME, Gould MS, Evans DB, Wolff RA, Crane CH: Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007;110:47–55.
- 36 Huguet F, André T, Hammel P, Artru P, Balosso J, Selle F, Deniaud-Alexandre E, Ruszniewski P, Touboul E, Labianca R, de Gramont A, Louvet C: Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326–331.
- 37 White RR, Xie HB, Gottfried MR, Czito BG, Hurwitz HI, Morse MA, Blobe GC, Paulson EK, Baillie J, Branch MS, Jowell PS, Clary BM, Pappas TN, Tyler DS: Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. *Ann Surg Oncol* 2005;12:214–221.
- 38 Chatterjee D, Katz MH, Rashid A, Varadhachary GR, Wolff RA, Wang H, Lee JE, Pisters PW, Vauthey JN, Crane C, Gomez HF, Abbruzzese JL, Fleming JB, Wang H: Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer* 2012;118:3182–3190.
- 39 Chen KT, Devarajan K, Milestone BN, Cooper HS, Denlinger C, Cohen SJ, Meyer JE, Hoffman JP: Neoadjuvant chemoradiation and duration of chemotherapy before surgical resection for pancreatic cancer: does time interval between radiotherapy and surgery matter? *Ann Surg Oncol* 2014;21:662–669.
- 40 Takai S, Sato S, Yanagimoto H, Toyokawa H, Takahashi K, Terakawa N, Araki H, Matsui Y, Sohga M, Kamiyama Y: Neoadjuvant chemoradiation in patients with potentially resectable pancreatic cancer. *Pancreas* 2008;36:e26–e32.
- 41 Sa Cunha A, Rault A, Laurent C, Adhoute X, Vendrely V, Béllannée G, Brunet R, Collet D, Masson B: Surgical resection after radiochemotherapy in patients with unresectable adenocarcinoma of the pancreas. *J Am Coll Surg* 2005;201:359–365.
- 42 Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, Rich TA, Adams RB, Bauer TW: Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. *Ann Surg Oncol* 2011;18:619–627.
- 43 Crane CH, Ellis LM, Abbruzzese JL, Amos C, Xiong HQ, Ho L, Evans DB, Tamm EP, Ng C, Pisters PW, Charnsangavej C, Delclos ME, O'Reilly M, Lee JE, Wolff RA: Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capecitabine in locally advanced pancreatic cancer. *J Clin Oncol* 2006;24:1145–1151.
- 44 Pisters PW, Wolff RA, Janjan NA, Cleary KR, Charnsangavej C, Crane CN, Lenzi R, Vauthey JN, Lee JE, Abbruzzese JL, Evans DB: Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 2002;20:2537–2544.
- 45 Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thielges S, Gawad KA, Schneider C, Izbicki JR: En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 2008;247:300–309.
- 46 Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, Gomez HF, Sun CC, Crane CH, Wolff RA, Evans DB: Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg* 2004;8:935–949; discussion 949–950.
- 47 Gawlas I, Epelboym I, Winner M, DiNorscia J, Woo Y, Lee JL, Schroepe BA, Chabot JA, Al-lendorf JD: Short-term but not long-term loss of patency of venous reconstruction during pancreatic resection is associated with decreased survival. *J Gastrointest Surg* 2014;18:75–82.
- 48 Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Büchler MW, Weitz J: Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882–893.
- 49 Bockhorn M, Burdelski C, Bogoevski D, Sgourakis G, Yekebas EF, Izbicki JR: Arterial en bloc resection for pancreatic carcinoma. *Br J Surg* 2011;98:86–92.
- 50 Willett CG, Del Castillo CF, Shih HA, Goldberg S, Biggs P, Clark JW, Lauwers G, Ryan DP, Zhu AX, Warshaw AL: Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. *Ann Surg* 2005;241:295–299.
- 51 Cai S, Hong TS, Goldberg SI, Fernandez-del Castillo C, Thayer SP, Ferrone CR, Ryan DP, Blaskowsky LS, Kwak EL, Willett CG, Lillemoe KD, Warshaw AL, Wo JY: Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978–2010. *Cancer* 2013;119:4196–4204.
- 52 Ruano-Ravina A, Almazán Ortega R, Guedea F: Intraoperative radiotherapy in pancreatic cancer: a systematic review. *Radiother Oncol* 2008;87:318–325.
- 53 Roldan GE, Gunderson LL, Nagorney DM, Martin JK, Ilstrup DM, Holbrook MA, Kvols LK, McIlrath DC: External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. *Cancer* 1988;61:1110–1116.
- 54 Zerbi A, Fossati V, Parolini D, Carlucci M, Balzano G, Bordogna G, Staudacher C, Di Carlo V: Intraoperative radiation therapy adjuvant to resection in the treatment of pancreatic cancer. *Cancer* 1994;73:2930–2935.
- 55 Alfieri S, Morganti AG, Di Giorgio A, Valentini V, Bossola M, Trodella L, Cellini N, Doglietto GB: Improved survival and local control after intraoperative radiation therapy and postoperative radiotherapy: a multivariate analysis of 46 patients undergoing surgery for pancreatic head cancer. *Arch Surg* 2001;136:343–347.
- 56 Ogawa K, Karasawa K, Ito Y, Ogawa Y, Jingu K, Onishi H, Aoki S, Wada H, Kokubo M, Etoh H, Kazumoto T, Takayama M, Negoro Y, Nemoto K, Nishimura Y; JROSG Working Subgroup of Gastrointestinal Cancers: Intraoperative radiotherapy for resected pancreatic cancer: a multi-institutional retrospective analysis of 210 patients. *Int J Radiat Oncol Biol Phys* 2010;77:734–742.
- 57 Valentini V, Calvo F, Reni M, Krempien R, Sedlmayer F, Buchler MW, Di Carlo V, Doglietto GB, Fastner G, Garcia-Sabrido JL, Mattiucci G, Morganti AG, Passoni P, Roeder F, D'Agostino GR: Intra-operative radiotherapy (IORT) in pancreatic cancer: joint analysis of the ISORT-Europe experience. *Radiother Oncol* 2009;91:54–59.

- 58 Sindelar WF, Kinsella TJ: Normal tissue tolerance to intraoperative radiotherapy. *Surg Oncol Clin N Am* 2003;12:925–942.
- 59 O'Connor JK, Sause WT, Hazard LJ, Belnap LP, Noyes RD: Survival after attempted surgical resection and intraoperative radiation therapy for pancreatic and periampullary adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2005;63:1060–1066.
- 60 Farrell TJ, Barbot DJ, Rosato FE: Pancreatic resection combined with intraoperative radiation therapy for pancreatic cancer. *Ann Surg* 1997;226:66–69.
- 61 Showalter TN, Rao AS, Rani Anne P, Rosato FE, Rosato EL, Andrel J, Hyslop T, Xu X, Berger AC: Does intraoperative radiation therapy improve local tumor control in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma? A propensity score analysis. *Ann Surg Oncol* 2009;16:2116–2122.
- 62 Al-Sakere B, André F, Bernat C, Connault E, Opolon P, Davalos RV, Rubinsky B, Mir LM: Tumor ablation with irreversible electroporation. *PLoS One* 2007;2:e1135.
- 63 Martin RC 2nd, McFarland K, Ellis S, Velanovich V: Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. *Ann Surg Oncol* 2013;20(suppl 3):S443–S449.
- 64 Kwon D, McFarland K, Velanovich V, Martin RC 2nd: Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation. *Surgery* 2014;156:910–920.
- 65 Mayo SC, Gilson MM, Herman JM, Cameron JL, Nathan H, Edil BH, Choti MA, Schulick RD, Wolfgang CL, Pawlik TM: Management of patients with pancreatic adenocarcinoma: national trends in patient selection, operative management, and use of adjuvant therapy. *J Am Coll Surg* 2012;214:33–45.
- 66 Barugola G, Partelli S, Crippa S, Butturini G, Salvia R, Sartori N, Bassi C, Falconi M, Pederzoli P: Time trends in the treatment and prognosis of resectable pancreatic cancer in a large tertiary referral centre. *HPB (Oxford)* 2013;15:958–964.
- 67 Kalser MH, Ellenberg SS: Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985;120:899–903.
- 68 Yeo CJ, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, Zahurak ML, Dooley WC, Coleman J, Sauter PK, Pitt HA, Lillemoe KD, Cameron JL: Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. *Ann Surg* 1997;225:621–633; discussion 633–636.
- 69 Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Büchler MW; European Study Group for Pancreatic Cancer: Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001;358:1576–1585.
- 70 Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004;350:1200–1210.
- 71 Stocken DD, Büchler MW, Dervenis C, Bassi C, Jeekel H, Klinkenbijl JH, Bakkevold KE, Takada T, Amano H, Neoptolemos JP; Pancreatic Cancer Meta-Analysis Group: Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005;92:1372–1381.
- 72 Chuong MD, Boggs DH, Patel KN, Regine WF: Adjuvant chemoradiation for pancreatic cancer: what does the evidence tell us? *J Gastrointest Oncol* 2014;5:166–177.
- 73 Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA: Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010;33:828–833.
- 74 Gemcitabine Hydrochloride with or without Erlotinib Hydrochloride Followed by the Same Chemotherapy Regimen with or without Radiation Therapy and Capecitabine or Fluorouracil in Treating Patients with Pancreatic Cancer That Has Been Removed by Surgery. <https://clinicaltrials.gov/ct2/show/NCT01013649>.